IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

EXELIXIS, INC.,

Plaintiff,

v.

MSN LABORATORIES PRIVATE LIMTED and MSN PHARMACEUTICALS, INC.,

Defendants.

Civil Action No. 19-2017-RGA-SRF

(Consolidated)

TRIAL OPINION

Jack B. Blumenfeld, Anthony D. Raucci, MORRIS, NICHOLS, ARSHT & TUNNELL LLP, Wilmington, DE; William F. Lee, Lisa J. Pirozzolo, Emily R. Whelan, Kevin S. Prussia, Timothy A. Cook, WILMER CUTLER PICKERING HALE AND DORR LLP, Boston, MA; Amy K. Wigmore, WILMER CUTLER PICKERING HALE AND DORR LLP, Washington, DC,

Attorneys for Plaintiff.

Dominick T. Gattuso, HEYMAN ENERIO GATTUSO & HIRZEL LLP, Wilmington, DE; George C. Lombardi, Bryson A. Cooper, Kurt A. Mathas, Jason Z. Pesick, Kevin J. Boyle, WINSTON & STRAWN LLP, Chicago, IL; Noorossadat Torabi, WINSTON & STRAWN LLP, San Francisco, CA,

Attorneys for Defendants.

January 19, 2023

ANDREWS, U.S. DISTRICT JUDGE:

Exelixis brought this action against MSN Laboratories Private Limited and MSN Pharmaceuticals, Inc. ("MSN") for infringement of U.S. Patent Nos. 7,579,473 ("'473 patent") and 8,877,776 ("'776 patent") under 35 U.S.C. § 271(e)(2)(A). (D.I. 270, Ex. 1, ¶¶ 7, 9). I held a four-day bench trial. (D.I. 297-300).[1] At trial, the parties disputed the validity of claim 5 of the '473 patent and the infringement of claim 1 of the '776 patent.

I have considered the parties' post-trial submissions. (D.I. 306, 307, 308, 309, 316, 317, 318, 319, 320, 321, 322). Having considered the documentary evidence and testimony, I make the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

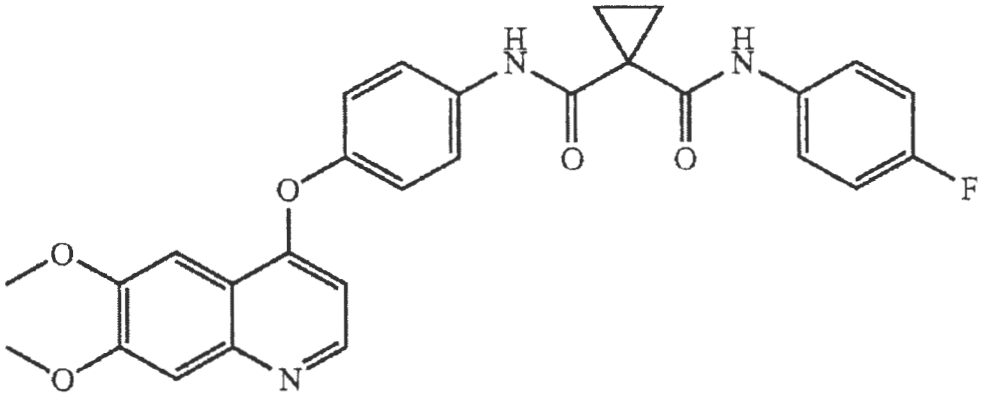
I. BACKGROUND

Exelixis is the holder of New Drug Application ("NDA") No. 208692 for Cabometyx®, a tablet containing the active pharmaceutical ingredient cabozantinib (S)-malate. (*See* D.I. 270, Ex. 1, ¶ 50). The Cabometyx® label states that cabozantinib (S)-malate inhibits the tyrosine kinase activity of certain tyrosine kinases, including c-Met. (*See id.*, Ex. 1, ¶¶ 28, 54). The FDA approved the use of Cabometyx® for treatment of select patients with advanced renal cell carcinoma, hepatocellular carcinoma, and differentiated thyroid cancer. (*See id.*, Ex. 1, ¶¶ 57-61).

The '473 and '776 patents are listed in the FDA's Orange Book for Cabometyx®. (*See id.*, Ex. 1, ¶ 66). The '473 patent discloses compounds including cabozantinib that are tyrosine kinase inhibitors ("TKIs"). (*See* JTX 3; D.I. 270, Ex. 1, ¶¶ 33-34). Salts of cabozantinib include cabozantinib (S)-malate and cabozantinib (L)-malate, which, for purposes of this decision, are

[1] I cite to the trial transcript as "Tr." The trial transcript is consecutively numbered.

synonymous. (*See* D.I. 270, Ex. 1, ¶¶ 73-74). The '776 patent is directed to a particular crystalline form of cabozantinib (L)-malate called Form N-2. (*See* JTX 1; D.I. 270, Ex. 1, ¶¶ 35, 40). The chemical structure of cabozantinib is:



(D.I. 270, Ex. 1, ¶ 17).

MSN submitted Abbreviated New Drug Application ("ANDA") No. 213878 under § 355(j) of the Federal Food, Drug, and Cosmetic Act seeking FDA approval to engage in the commercial manufacture, use, or sale of cabozantinib tablets ("MSN's proposed ANDA product" or "MSN's tablets"). (*See id.*, Ex. 1, ¶ 67). In so doing, MSN filed certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) ("Paragraph IV certifications") for both the '776 and '473 patents. (*See id.*, Ex. 1, ¶¶ 6, 8). Exelixis received notice of MSN's Paragraph IV certifications and initiated the present lawsuit. (*See id.*, Ex. 1, ¶¶ 7, 9).

II. INVALIDITY OF THE '473 PATENT

A. Legal Standard

A patent claim is invalid as obvious under 35 U.S.C. § 103 "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103. "Under § 103, the scope

and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007) (cleaned up).

"[W]hether a new chemical compound would have been *prima facie* obvious over particular prior art compounds ordinarily follows a two-part inquiry." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). "First, the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Id.* A lead compound is "a compound in the prior art that would be most promising to modify in order to improve upon its … activity and obtain a compound with better activity." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). "In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties" including "positive attributes such as activity and potency" and "adverse effects such as toxicity." *Otsuka*, 678 F.3d at 1292. Second, the court determines "whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Id.*

A court is also required to consider "the [secondary considerations] before reaching an obviousness determination … as a check against hindsight bias." *In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Pat. Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject

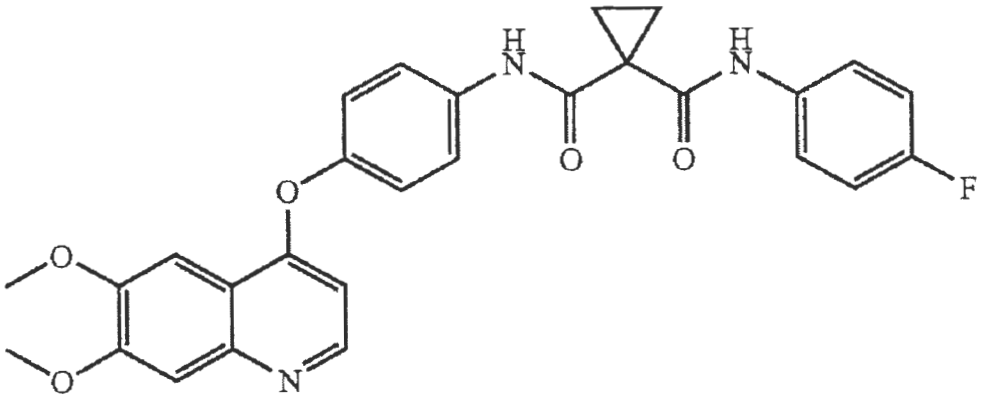
matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

MSN has the burden of proving obviousness by clear and convincing evidence. *See Otsuka*, 678 F.3d at 1292.

B. Asserted Claim of the '473 patent

Claim 5 of the '473 patent requires the chemical structure of cabozantinib or a pharmaceutically acceptable salt thereof. Claim 5 states:

5. A compound represented by the structure:



or a pharmaceutically acceptable salt thereof.

(JTX 3 at 412:34-51 (claim 5), p. 209 (Certificate of Correction), p. 211 (Certificate of Correction)).

C. Findings of Fact

1. A person of ordinary skill in the art (POSA) would have had, at the time of the claimed invention, a doctorate degree in chemistry, molecular biology, pharmacology, medicine, or a related discipline, with two to three years of experience in one or more of the following areas: medicinal chemistry, biology and/or pharmacology relating to tyrosine kinases and inhibitors thereof, structure-activity relationships, and treatment of cancer. Alternatively, a POSA may have had a lesser post-graduate degree in one of those fields, with at least five years of experience in the same areas. To the extent necessary, a POSA may have collaborated with others of skill in the art, such that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds, preparing pharmaceutical formulations containing an excipient and an active pharmaceutical ingredient, and treating cancer patients. (*See* D.I. 270, Ex. 1, ¶ 24; *see also* Tr. at 412:19-22 (Lepore), 519:1-14 (Mega), 537:24-538:1 (George), 664:1-6 (MacMillan)).

2. Claim 5 of the '473 patent has a priority date of September 26, 2003. (D.I. 270, Ex. 1, ¶ 22).

3. A POSA would have been aware of research involving targeted cancer therapies, including TKIs that inhibit c-Met. (*See* Tr. at 529:3-17 (Mega), 594:17-19 (George); DTX-17.2 (Traxler) at Table 1; DTX-37 (Maulik) at 16; DTX-66 (Oliff) at 1, 5).

4. Kirin (DTX-6) is prior art to the '473 patent.

5. A POSA would have considered Kirin when pursuing TKIs that inhibit c-Met. (*See* Tr. at 430:20-431:5 (Lepore)).

6. Kirin discloses 333 "preferred compounds" that inhibit c-Met. (*See id.* at 677:17-22 (MacMillan); DTX-6 at 4 (describing compounds that "act[] to inhibit met autophosphorylation and [have] antitumor effects"), 22-50 (listing the 333 compounds)). Kirin's 333 exemplified compounds fall into five buckets: 160 thioureas, 99 ureas, 42 biurets, 31 malonamides, and one amide. (*See* Tr. at 681:22-682:11 (MacMillan); DTX-6 (Kirin) at 22-50).

7. Kirin's preferred compound 5 ("Example 5") is a malonamide. (*See* Tr. at 439:5-6 (Lepore); DTX-6 at 22).

8. A POSA reviewing Kirin would have recognized a general preference for the use of thioureas and ureas as c-Met inhibitors. (*See generally* Tr. at 680:23-693:24 (MacMillan); *see also* Tr. at 479:1-23 (Lepore)).

9. Considering Kirin, a POSA would not have categorically deprioritized all of its exemplary thioureas when identifying lead compounds. (*See* Tr. at 682:20-684:9,

695:1-696:12 (MacMillan); DTX-6 (Kirin) at 4; DTX-18 (Onderwater 1998) at 2, 11; *see also* Tr. at 703:1-11 (MacMillan)).

10. Considering Kirin, a POSA would not have deprioritized the ureas that were more potent than Example 5. (*See* Tr. at 688:1-11 (MacMillan); *see also* Tr. at 449:9-16 (Lepore)).

11. Considering Kirin, a POSA would not have prioritized Example 5 over the more-potent Kirin's preferred compound 269 ("Example 269"). (*See* Tr. at 699:21-701:20 (MacMillan)).

12. Considering Kirin, a POSA would not have identified Example 5 as a lead compound. (*See id.* at 693:25-694:6 (MacMillan))

13. A POSA would not have been motivated to modify Example 5 to include a cyclopropyl group because this modification would have unpredictably altered the compound's functionality and ability to inhibit c-Met. (*See id.* at 705:5-708:18, 711:5-24 (MacMillan)).

14. A POSA would not have been motivated to modify Example 5 to include a cyclopropyl group because this modification would have caused the POSA to have concerns regarding toxicity. (*See id.* at 672:22-673:6 (MacMillan)).

15. A POSA would not have been motivated to modify Example 5 to include a cyclopropyl group because this modification would have caused them to have concerns regarding a reduction in potency. (*See id.* at 706:8-12, 709:5-711:4, 719:21-25 (MacMillan)).

16. A POSA would not have been motivated to modify Example 5 to pursue an irreversible inhibitor. (*See id.* at 572:4-20 (George), 711:5-24, 715:19-716:5, 731:9-20 (MacMillan)).

17. A POSA would not have had a reasonable expectation that modifying Example 5 to include a cyclopropyl group would be successful due to the unpredictability in making this modification. (*See id.* at 718:13-720:15 (MacMillan); *see also id.* at 461:7-12, 463:2-463:8 (Lepore)).

D. Conclusions of Law

MSN argues that claim 5 of the '473 patent is invalid as obvious based on a lead compound analysis. For the following reasons, MSN has not presented clear and convincing evidence of obviousness. Based on my factual findings, a POSA would not have been motivated to select

Kirin's Example 5 as a lead compound. Furthermore, even if Example 5 was selected as a lead compound, a POSA would not have found it obvious to modify Example 5 to reach cabozantinib.

1. Selecting Example 5 of Kirin as a Lead Compound

MSN argues, "a POSA would have been motivated to inhibit c-Met to treat cancer" and, with that motivation, would have "selected Kirin Example 5 as a lead compound" for further development. (D.I. 307 at 4-5).

MSN asserts that, at the time of the invention, a POSA would have known "that inhibiting tyrosine kinases could treat a variety of cancers" and that "many pharmaceutical companies … were developing [TKIs] to treat cancer." (D.I. 307 at 5-9, 5; *see also* DTX-66 (Oliff) at 1 (describing "new molecular targets for cancer therapy"), 5 (listing TKIs as one of multiple targeted cancer therapies being considered)). MSN argues that c-Met is a tyrosine kinase that researchers would have been motivated to research how to inhibit. (*See* D.I. 307 at 7-8; *see also* Tr. at 529:3-17 (Mega), 594:17-19 (George); DTX-17 (Traxler) at 2 (listing "c-Met" as one of "more than 20 different tyrosine kinase targets [that] are under evaluation in drug discovery projects in oncology"), 13; DTX-37 (Maulik) at 16 ("c-Met serves as an attractive target for molecularly targeted therapy"); DTX-39 (Shawver) at 5).

With that motivation, MSN explains that, at the time of the invention, Kirin was "the only prior art reference that disclosed specific exemplified small-molecule c-Met inhibiting compounds." (D.I. 307 at 11 (citing Tr. at 430:20-25 (Lepore), 735:5-9 (MacMillan)). Kirin discloses 333 "preferred compounds" that inhibit c-Met. (DTX-6 at 4, 22-50; *see also* Tr. at 677:17-22 (MacMillan)). Thus, MSN argues, "following the motivation … to pursue a c-Met inhibitor to treat cancer[,]" a POSA "would have chosen a lead compound from the Kirin Publication." (D.I. 307 at 11 (citing Tr. at 431:1-5 (Lepore))).

Exelixis disagrees, arguing that, at the time of the invention, a POSA would have been aware that "researchers had identified many different types of targeted therapies to treat cancer [of which] tyrosine kinase inhibition represented just one approach[.]" (D.I. 316 at 4-7, 4; *see also* Tr. at 559:21-560:22 (George)). Further, Dr. George explained that, even within the class of TKIs, there were "more than 20 different kinase targets [other than c-Met that were] under evaluation[.]" (Tr. at 563:3-22 (George); *see also* Tr. at 525:12-22 (Mega), 566:14-567:5 (George)). Based on this, Dr. George testified that there would have been "no motivation to pursue a c-Met inhibitor compared with other better-known targets at the time." (*Id.* at 594:3-8 (George); *see also id.* at 570:5-572:3 (George)). Thus, Exelixis argues that MSN's "focus[] specifically on a c-Met inhibitor" is based "on 'an overly narrow statement of the problem'" that improperly relies on hindsight. (D.I. 316 at 6-7, 7 (quoting *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015)).

Additionally, even if a POSA were motivated to pursue a c-Met inhibitor over other targeted cancer treatments, Exelixis argues that the POSA would not have gravitated towards Kirin because "Kirin does not include any clinical data for [its] exemplified c-Met inhibitors, nor does the reference describe any c-Met inhibitors in clinical development." (D.I. 316 at 8; *see also* Tr. at 676:24-677:22 (MacMillan)).

I find that MSN has shown that a POSA would have considered c-Met inhibitors as an avenue for further development in targeted cancer treatment. (*See* Tr. at 594 at 17-19 (George) (agreeing that "as of 2003, … there was a motivation to pursue c-Met inhibitors"); *see also* D.I. 320 at 1-4). I do not agree that a POSA would overlook c-Met inhibitors in their entirety due to additional, potentially more promising, directions for research. *See Insite Vision*, 783 F.3d at 560 ("Whether a person of ordinary skill in the art would narrow the research focus to lead to the

invention depends on the facts."). Similarly, I find that a POSA would have considered Kirin, which Dr. Lepore credibly testified as being "the only publication that disclosed small molecule inhibitors of c-Met." (Tr. at 430:20-25 (Lepore)).

MSN next argues that a POSA, considering the exemplary compounds listed in Kirin, "would have identified Kirin Example 5 as the most promising lead compound, because it had the best mixture of the desirable properties a medicinal chemist would have been looking for in drug development." (D.I. 307 at 11). In identifying a lead compound, MSN contends that a POSA would have prioritized compounds with high potency, high bioavailability, low toxicity, and the potential for irreversible inhibition. (*See* D.I. 307 at 10 ("a POSA would have been motivated to pursue an irreversible inhibitor" because they require "smaller and fewer doses" than reversible inhibitors) (citing DTX-13.194 (Silverman); DTX-30 (Fry) at 5 ("the property of irreversibility confers a significant therapeutic advantage over equally potent reversible analogs"); Tr. at 420:25-424:13, 424:6-13 (Lepore) ("a POSA would have thought that irreversible inhibition by tyrosine kinases was a desirable thing")); D.I. 307 at 12-13 (arguing that a POSA would have considered "potency, bioavailability, and toxicity") (citing Tr. at 414:14-23 (Lepore), 666:4-15 (MacMillan))).

Specifically, MSN argues that, considering Kirin, a POSA would have started with the exemplary compounds with the highest potency, then narrowed them down based on toxicity, bioavailability, and potential for irreversible inhibition. (*See* D.I. 307 at 14-16). For each of the 333 exemplary compounds, Kirin provides an "IC_{50} value" representative of potency. (DTX-6 (Kirin) at 387-389 (Table 2); *see also* D.I. 307 at 13 (citing Tr. at 431:1-17 (Lepore))). Many of the most potent exemplary compounds, as measured by their IC_{50} values, are thioureas. (*See* D.I. 307 at 14). According to Dr. Lepore, however, a POSA "would have thought that these [thiourea]

compounds may have … toxicity issues [and would have] deprioritized [them] in terms of coming up with a … lead compound." (Tr. at 437:12-20 (Lepore); *see also* D.I. 307 at 14-15 (citing Tr. at 433:9-434:3, 436:22-437:20 (Lepore); DTX-18 (Onderwater 1998) at 2; DTX-19 (Onderwater 1999) at 1 ("some [Thiourea-containing compounds] also cause hypersensitivity reactions, and are pulmonary toxins or hepatotoxins"))).

Excluding the thioureas, the most potent of Kirin's remaining exemplary compounds include a malonamide (Example 269), two urea compounds, and, in the fourth position, another malonamide (Example 5). (*See* D.I. 307 at 15-16). Of these compounds, MSN asserts that a POSA would have deprioritized the urea compounds because they would "not provide an opportunity for irreversible inhibition[.]" (*Id.* at 15-16 (citing Tr. at 438:25-439:11 (Lepore))).

Dr. Lepore testified that a POSA would have known that malonamides, unlike the ureas, have the "potential for irreversible inhibition." (Tr. at 439:3-7 (Lepore)). Between Example 269 and Example 5, MSN argues that a POSA would have deprioritized Example 269 because, while more potent and potentially irreversible, "a POSA would have understood … that it did not have a desirable oral bioavailability profile based on the … Lipinski criteria." (D.I. 307 at 15 (citing Tr. at 437:21-439:10 (Lepore) (describing Example 269 as "a big compound" that would have "Lipinski's rule concerns"), 753:25-754:5 (MacMillan))). On the other hand, MSN contends that a POSA would have identified Example 5 as a lead compound because, while less potent than Example 269, it "would have been predicted to be more orally bioavailable[,]" and, unlike the ureas, it had the "potential to be an irreversible inhibitor[.]" (D.I. 307 at 15-16 ("Example 5 [had] an optimal mix of characteristics") (citing Tr. at 438:25-439:25, 441:5-16 (Lepore))).

I am not convinced that a POSA would have identified Example 5 as a lead compound. Overall, MSN's iterative deprioritization of the 14 compounds that are more potent than Example

5 appears to rely on improper hindsight. (*See KSR*, 550 U.S at 421 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."); *Otsuka*, 678 F.3d at 1294 ("[W]e focus in particular on the compounds' disclosed properties because …, generally, a skilled artisan would be attracted to the most potent compounds in selecting a lead compound for development.") (cleaned up); *see also* Tr. at 688:15-19 (MacMillan)).

To start, a POSA reviewing Kirin would have recognized a general preference for the use of compounds other than malonamides (such as Example 5) as c-Met inhibitors. (*See generally* Tr. at 680:23-693:24 (MacMillan)). Kirin lists 333 exemplary compounds, of which only 31 are malonamides. (*See* DTX-6 at 384-385, 389-393). Further, Kirin identifies five compounds as "most preferred," none of which are malonamides. (*See id.* at 50 ("Examples of most preferred compounds … include ….")). Three of the most preferred compounds were thioureas. (*See* Tr. at 479:1-23 (Lepore)). Even more, while disclosing in vitro test results for all 333 exemplified compounds, Kirin provides in vivo test results for only 23 compounds, none of which are malonamides. (*See* DTX-6 at 384-385, 389-393). In vivo testing provides a better approximation of how each compound would work in humans. (*See* Tr. at 688:22-690:19 (MacMillan)). Dr. MacMillan credibly testified that a POSA would have understood that Kirin was "prioritizing [the] molecules [that] were being examined [in vivo]." (*Id.* at 689:7-13).

I find that MSN overreached in its categorical deprioritization of thioureas based on potential toxicity concerns. (*See id.* at 696:6-12 (MacMillan)). Kirin clearly posits numerous thioureas as potential pharmaceutical compounds "having potent antitumor activity." (DTX-6 at 4; *see also* Tr. at 682:20-684:9 (MacMillan); DTX-6 at 50). Dr. MacMillan also explained that, at the time of the invention, there were multiple thioureas in clinical use or trials. (*See* Tr. at

695:1-11 (MacMillan)). Indeed, Dr. MacMillan credibly testified that even Onderwater 1998, on which Dr. Lepore relied to support thioureas being toxic, describes "us[ing] thioureas for drug molecules for human beings." (*Id.* at 695:1-696:5 (MacMillan); *see also* DTX-18 (Onderwater 1998) at 2 (suggesting a need to "clarify … thiourea toxicity" to develop "a more rational design of thiourea-containing drugs and drug candidates" and describing the use of thioureas "in the treatment of Graves' disease [and in] clinical trials for the treatment of AIDS"), 11).

Furthermore, while Dr. Lepore found that Kirin's thioureas should be categorically deprioritized based on potential toxicity concerns, Dr. Lepore was more forgiving with the flaws he found in Example 5, as is discussed in more detail below. (*See infra* Section II.D.2). When Dr. Lepore found Example 5 to be metabolically unstable, he did not simply exclude it. Instead, he relied on this flaw as a motivation to modify Example 5. (*See id.*). I find persuasive Dr. MacMillan's testimony that metabolic instability relates to toxicity (*see* Tr. at 702:14-25), so this is "almost saying, I'm going to throw out a whole class of compounds to focus on a molecule that [also] has a problem." (Tr. at 703:1-11).

Thus, for Dr. Lepore to base his obviousness analysis on Kirin, only to disregard all of Kirin's preferred thioureas, at best suggests hindsight bias and at worst a lack of credibility.

Next, I disagree with MSN's deprioritization of the ureas based on concerns that a POSA would not want to experiment with compounds that would be unable to form irreversible inhibitors. Kirin clearly presents not only thioureas but also ureas as preferred compounds for further development. (*See* DTX-6 (Kirin) at 50, 385-389). Thus, Kirin suggests either that ureas were thought to be able to form irreversible inhibitors or that was not a great concern to a POSA. But even if a POSA would have a strong interest in a compound with the potential for irreversible inhibition, that would not justify eliminating ureas. Dr. MacMillan credibly testified that a POSA

"could take [the ureas] and [modify them to] make them irreversible inhibitors." (Tr. at 688:1-11). The fact that ureas may have potential for irreversible inhibition is particularly prescient when considering that Dr. Lepore suggested that a POSA, after selecting Example 5 as a lead compound, would be motivated to modify it to give "the molecule the potential for irreversible inhibition." (Tr. at 449:9-16 (Lepore); *see infra* Section II.D.2). I do not find credible that Dr. Lepore would throw out the more-potent ureas due to a lack of potential for irreversible inhibition only to suggest modifying the less-potent Example 5 due to it also lacking potential for irreversible inhibition.

Finally, I disagree with Dr. Lepore passing on the more-potent Example 269 before reaching Example 5. While Dr. Lepore deprioritized Example 269 based on a violation of Lipinski's criterion for molecular weight, Dr. MacMillan testified that a POSA would not rely on this criterion alone as a gatekeeper in selecting a lead compound. (*See* Tr. at 699:21-701:20). Instead, Lipinski's criteria provide five rules, of which a compound must fail two or more to spark concern. (*See* Tr. at 699:21-700:16 (MacMillan)). Dr. MacMillan convincingly testified that, while Example 269 does not meet Lipinski's criteria for molecular weight, a POSA would not have been troubled because only one of Lipinski's criteria was violated. (*See* Tr. at 700:17-701:20, 700:11-13 ("When you look at Compound 269, only one of those [Lipinski's criteria] falls out. So, it would not raise a flag.")). Instead, a POSA would have preferred Example 269 as the more potent compound. *See Daiichi Sankyo Co. v. Matrix Lab'ys, Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) ("Potent and promising activity in the prior art trumps mere structural relationships.").

Thus, considering the evidence, I find that MSN has not shown by clear and convincing evidence that a POSA would have identified Example 5 as a lead compound. "While the lead

compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound, … the analysis still requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art." *Id.*

2. Modifying Example 5 to Form Cabozantinib

MSN next argues that a POSA would have been motivated to modify Example 5 "to arrive at cabozantinib, with a reasonable expectation of obtaining a c-Met inhibitor." (D.I. 307 at 5). MSN's argument hinges on whether a POSA would have identified Example 5 as a lead compound, which I have already rejected. There is another hurdle, however, even if a POSA identified Example 5 as a lead compound. MSN does not meet that hurdle. I find that MSN has not shown by clear and convincing evidence that a POSA would have been motivated to modify Example 5 to reach cabozantinib.

MSN argues, "a POSA would have been motivated to [modify Example 5] to improve the compound's metabolic stability and to increase the potential for irreversible inhibition." (*Id.* at 16-17). Specifically, Dr. Lepore testified that a POSA would have been concerned that two carbon-hydrogen bonds in Example 5's malonamide group could cause it to "go to … a potentially unstable form[.]" (Tr. at 442:4-15 (referencing DTX-23.2 (Williams)); *see also* Tr. at 758:13-759:3 (MacMillan) (agreeing that "a POSA would have understood the potential for Kirin Example 5 to be metabolically unstable")). MSN asserts that a POSA would have known that replacing the two carbon-hydrogen bonds with a cyclopropyl group, thereby forming cabozantinib, would cure this instability. (*See* D.I. 307 at 19-20 (citing Tr. at 442:25-443:7, 444:9-15, 449:4-9 (Lepore); *see also* Tr. at 443:8-24 (Lepore) (explaining that this modification would "not unduly increase the molecular weight" of the compound)). Dr. Lepore testified that an added motivation

for incorporating the cyclopropyl group "would have given to the molecule the potential for irreversible inhibition." (Tr. at 449:9-16 (Lepore); *see also* D.I. 307 at 20-21; Tr. at 424:14-426:5, 445:16-447:16 (Lepore); DTX-27.1 (Kelner); DTX-25.4 (McMorris); DTX-28.2 (Salaun)).

Dr. Lepore also explained that a POSA would have had a reasonable expectation that, after making this modification, the molecule would still "have activity to inhibit the c-Met biological target." (Tr. at 448:2-449:16, 449:4-16; *see also* D.I. 307 at 19-20).

I disagree that a POSA would have been motivated to modify Example 5 to include a cyclopropyl group. MSN's reasoning is flawed for at least two reasons: a POSA would have been concerned that this modification would have unpredictable effects, and a POSA would not have been motivated to pursue an irreversible inhibitor. (*See generally* D.I. 316 at 14-21).

I find that modifying Example 5 to include a cyclopropyl group could unpredictably alter the compound's functionality, toxicity, and potency.

First, a POSA would not have understood how modifying Example 5 would alter the compound's functionality. Dr. MacMillan explained that, due to the bonds involved, adding a cyclopropyl group would "change the three-dimensional shape of Kirin Compound 5." (Tr. at 705:5-707:19, 707:17-19 (MacMillan)). Dr. MacMillan persuasively testified that, considering the structure of c-Met was unknown in 2003, a POSA would not have been able to predict how altering the structure of Example 5 would affect its ability to inhibit c-Met. (*See* Tr. at 707:20-708:18; *see also* Tr. at 711:5-24 (MacMillan) (explaining that McMorris (DTX-25) and Kelner (DTX-27) describe a different class of molecules than Example 5 and, thus, Dr. Lepore's reliance on these references to support his argument that modifying Example 5 would form an irreversible inhibitor was misguided)).

Second, a POSA would have had concerns that this modification could lead to toxicity. Dr. MacMillan testified persuasively that modifying Example 5 to include the cyclopropyl group would make the compound "extremely reactive" and that this would cause a POSA to "have significant concerns about … toxicity." (Tr. at 672:22-673:6).

Third, a POSA would have had concerns that this modification would decrease potency. MSN proposes modifying Example 5 by adding a cyclopropyl group at the position of the malonamide. Dr. MacMillan explained that a POSA would have understood from analyzing the compounds listed in Kirin "that when you introduce groups at that position of a malonamide, that the potency would actually diminish." (*Id.* at 719:21-25; *see also id.* at 706:8-12, 709:5-711:4). Thus, Dr. MacMillan persuasively testified that a POSA would have had "significant concerns" that MSN's proposed modification would lead to a reduction in potency. (*Id.* at 711:2-4).

I find that a POSA would have had substantial concerns with the risks associated with irreversible inhibitors and would not have pursued this feature without reservations. Dr. MacMillan explained that irreversible inhibitors may target both cancerous and healthy cells, thus having a "very significant" potential for toxicity. (*Id.* at 715:19-716:5; *see also id.* at 731:9-20 (MacMillan)). Similarly, Dr. George explained that the target of an inhibitor could also be "important to the blood supply to the body," where, if an irreversible inhibitor is used, it could also cause irreversible side effects. (*Id.* at 572:4-20). I find the testimony of Dr. MacMillan and Dr. George on this point to be compelling, particularly when considering the lack of clear evidence regarding whether a POSA would expect this modification to form an irreversible inhibitor. (*See, e.g.*, *id.* at 711:5-24 (MacMillan) (explaining deficiencies in references Dr. Lepore relied on related to irreversibility)).

I also find that MSN has not proven that a POSA would have had a reasonable expectation of success in performing MSN's proposed modification due to the modification's unpredictability. (*See id.* at 718:13-720:15; *see also* D.I. 316 at 19-21). Dr. MacMillan credibly testified that a POSA would not have had a reasonable expectation of success due to the "difficult[y] [in] know[ing] what [was] going to happen." (Tr. at 719:13-15). Even Dr. Lepore conceded, "one didn't know for sure" whether the modification would result in an irreversible inhibitor. *(Id.* at 463:2-463:8 (Lepore); *see also id.* at 714:18-715:12 (MacMillan); 806:9-23 (Mega)). Confirming this unpredictability, the modified compound (cabozatinib) is not an irreversible inhibitor. (*See id.* at 461:7-12 (Lepore)).

For these reasons, I find that MSN has not proven by clear and convincing evidence that a POSA would have been motivated to modify Example 5 to form cabozantinib. While MSN argues that this modification would improve stability, I do not find that MSN has proven that this improvement could justify the substantial risks outlined in Dr. MacMillan's testimony. (*See, e.g.*, *id.* at 672:22-673:6, 707:20-711:4 (MacMillan)). Additionally, while MSN presents a POSA's desire for a "potential" irreversible inhibitor as a secondary motivation, MSN's evidence is unpersuasive and questionable considering the persuasive testimony of Dr. MacMillan and Dr. George.

The parties also dispute whether secondary considerations would offer support that the asserted claim is not obvious. I do not need to address the secondary considerations. Generally, when secondary considerations are proven, that helps the patentee in an obviousness analysis. When they are unproven, then secondary considerations are neutral, and they do not impact the analysis. Since, even if I were to agree with MSN that they were entirely unproven, I would still, and do, find that MSN has not proved obviousness by clear and convincing evidence.

I therefore find that MSN has not shown by clear and convincing evidence that claim 5 of the '473 patent is invalid as obvious.

III. INFRINGEMENT OF THE '776 PATENT

A. Legal Standard

A patent is directly infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent." 35 U.S.C. § 271(a). Determining infringement is a two-step analysis. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *See id.* This second step is a question of fact. *See Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998). The patent owner bears the burden of proving infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab'ys Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

In a Hatch-Waxman case, the plaintiff's infringement claim is based on the accused infringer's future conduct, rather than past acts of infringement. Under § 271(e)(2), the "infringement inquiry … is focused on the product that is likely to be sold following FDA approval." *Abbott Lab'ys v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). "Because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with the ANDA's description of the drug, an ANDA specification defining a proposed generic drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." *Id.*

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). To prevail on a claim of induced infringement, the plaintiff must show (1) "that there has been direct infringement," and (2) "that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *Enplas Display Device Corp. v. Seoul Semiconductor Co.*, 909 F.3d 398, 407 (Fed. Cir. 2018) (cleaned up). In a Hatch-Waxman case, a plaintiff "can satisfy its burden to prove the predicate direct infringement by showing that if the proposed ANDA product were marketed, it would infringe the [asserted claim]." *Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1130 (Fed. Cir. 2018).

B. Asserted Claim of the '776 patent

Claim 1 of the '776 patent states:

> 1. N-(4-{[6,7-bis(methyloxy)quinolin-4-yl]oxy}phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (L)-malate salt, wherein said salt is in crystalline Form N-2 and said Form N-2 is characterized by at least one of the following:
>
> (i) solid state ^{13}C NMR spectrum with four or more peaks selected from 23.0, 25.9, 38.0, 41.7, 69.7, 102.0, 122.5, 177.3, 179.3, 180.0, and 180.3, ±0.2 ppm;
>
> (ii) a powder x-ray diffraction pattern (CuKα λ=1.5418 Å) comprising 2θ values at 20.9±0.2 °2θ and 21.9±0.2 °2θ, and two or more 2θ values selected from: 6.4±0.2 °2θ, 9.1±0.2 °2θ, 12.0±0.2 °2θ, 12.8±0.2, 13.7±0.2, 17.1±0.2, 22.6±0.2, 23.7±0.2, wherein measurement of the crystalline form is at room temperature; and/or
>
> (iii) an x-ray powder diffraction (XRPD) pattern substantially in accordance with the pattern shown in FIG. 8.

(JTX-1 at 30:66-31:14 (claim 1)).

C. Findings of Fact

1. A POSA would have had at least a bachelor's degree in chemistry, chemical engineering, pharmaceutical sciences, or a related discipline, along with several years of experience working in pharmaceutical development and/or solid state chemistry and would also have been part of a team which would have included synthetic organic

chemists and process chemists, formulation scientists, analytical scientists, and clinicians. (*See* D.I. 270, Ex. 1, ¶ 46).

2. MSN's active pharmaceutical ingredient ("API"), will be stored "in well closed containers at 2 to 8°C temperature and protect[ed] from moisture." (PTX-123 at 25).

3. The samples of MSN's API that Dr. Munson tested were three years old when he received them. (*See* Tr. at 230:8-17 (Munson); 301:20-24 (Steed)).

4. The conditions that MSN's API will face during manufacture are not representative of the conditions that MSN's API will likely face after it is manufactured. (*See id.* at 327:20-328:3 (Steed)).

5. Dr. Munson's accelerated conditions are not representative of the prescribed storage conditions of MSN's API prior to tablet manufacturing. (*See id.* at 230:8-17 (Munson), 301:20-24, 305:19-306:5, 315:18-316:15, 331:3-6 (Steed); PTX-123 at 25).

6. MSN's API will be combined with excipients before the granulating, drying, and coating steps of MSN's tablet manufacturing begin. (*See* PTX-67 at 2-3). Excipients can act to stabilize an API. (*See* Tr. at 316:18-317:1; 320:2-9, 323:1-5 (Steed)).

7. Dr. Munson's accelerated conditions are not representative of the conditions that MSN's API will undergo during tablet manufacturing. (*See id.* at 317:2-323:24 (Steed))

8. The product label for MSN's tablets will require storing "cabozantinib at room temperature between 68°F to 77°F (20°C to 25°C)." (PTX-114 at 24).

9. Dr. Munson's accelerated conditions are not representative of the conditions MSN's tablets will likely face. (*See* Tr. at 339:12-22, 342:17-20, 403:16-24 (Steed)).

10. Dr. Munson's testing of MSN's API after applying accelerated conditions is not an accurate predictor of how MSN's API will change over time. (*See id.* at 314:3-318:10, 328:8-13 (Steed)).

11. Stability studies, such as those pursuant to the guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use ("ICH"), are not always predictive of physical changes that compounds will experience over time. (*See* PTX-739 at 13; *see also* DTX-484 at 50).

12. For stability testing of a refrigerated compound, the ICH guidelines recommend accelerated conditions of "25°C ± 2°C/60% RH ± 5% RH." (PTX-739 at 10). For

stability testing a new drug compound, the ICH guidelines recommend using a closed container "that is the same as or simulates the packaging proposed for storage and distribution." (*Id.* at 8).

13. Dr. Munson's accelerated conditions are not representative of the conditions that the ICH guidelines recommend for testing a new drug compound that should be refrigerated. (*See* Tr. at 333:7-13 (Steed)).

14. MSN performed stress testing on its API in the process of developing a manufacturing process. (*See id.* at 324:4-325:12 (Steed)). The conditions used by MSN in this testing are not representative of conditions that MSN's API or tablet will likely face. (*See* Tr. at 324:4-325:25, 400:4-10 (Steed)).

15. ^{19}F SSNMR testing is a more sensitive technique than ^{13}C NMR testing for measuring the presence of Form N-2 in MSN's API. (*See id.* at 131:4-20 (Munson)).

16. Dr. Munson's ^{19}F SSNMR testing of MSN's API using his accelerated conditions did not reasonably quantify the amount of Form N-2 that was initially present in MSN's API. (*See id.* at 179:1-13, 221:17-222:7 (Munson)).

17. MSN's API and proposed ANDA product will not infringe claim 1 of the '776 patent.

D. Conclusions of Law

For infringement of claim 1 of the '776 patent, Exelixis must prove that Form N-2 will be detected in MSN's proposed ANDA product according to ^{13}C NMR test criteria (limitation 1(i)) and/or XRPD test criteria (limitations 1(ii) or 1(iii)). (*See* JTX-1 at 30:66-31:14). MSN contends that its tablets will include only Form S of cabozantinib, where MSN formulated Form S as a design around for Form N-2. (*See* D.I. 319 at 1). Exelixis disagrees, arguing that Form S is unstable and, over time, will convert to Form N-2, thus causing infringement. (*See* D.I. 308 at 2; D.I. 319 at 2). The parties dispute whether Exelixis has proven by a preponderance of the evidence that MSN's tablets, which will be manufactured using Form S as the API, will infringe limitation 1(i) of claim 1. For the reasons described below, I find that Exelixis has failed to meet its burden.

1. Exelixis' ^{13}C NMR Testing of MSN's API Under Accelerated Conditions

At trial, Exelixis provided no direct evidence of ^{13}C NMR or XRPD test results detecting Form N-2 in MSN's tablets. (*See* D.I. 308 at 4 ("Dr. Munson did not directly detect Form N-2 in MSN's Tablets")). Instead, Exelixis presented evidence that Dr. Munson detected Form N-2 in MSN's API through ^{13}C NMR testing. (*See id.* at 13-14 (citing D.I. 309, ¶¶ 57-58)). Dr. Munson's testing of MSN's API did not detect Form N-2 in MSN's three-year-old as-provided samples, however. (*See id.*). Dr. Munson only detected Form N-2 in MSN's API after subjecting the test samples to "accelerated conditions." (*See id.*). The parties disagree whether Dr. Munson's accelerated conditions are representative of the conditions MSN's proposed ANDA product will likely face in the real world and, thus, if the corresponding test results are indicative of infringement of claim limitation 1(i). *See Merck Sharp & Dohme Corp. v. Amneal Pharms. LLC*, 881 F.3d 1376, 1385 (Fed. Cir. 2018) ("[T]he critical inquiry is whether [the tested sample] is representative of what is likely to be approved and marketed.").

Exelixis explains that Dr. Munson subjected MSN's API to accelerated conditions of 40°C at 75% relative humidity ("RH") in an open container. (*See* D.I. 308 at 10, 17 (citing D.I. 309, ¶¶ 55, 57-58)). Dr. Munson then performed ^{13}C NMR testing on the conditioned API after four and eight weeks, and, in both tests, detected Form N-2. (*See id.* at 10, 13-14 (citing D.I. 309, ¶¶ 57-58)).

Exelixis argues that Dr. Munson's ^{13}C NMR testing of MSN's API after applying the accelerated conditions is representative of how the API "will behave in the real world over time[.]" (*Id.* at 3-4, 13-18). Specifically, Exelixis contends that the accelerated conditions "expose the API … to a variety of conditions that [it] will most likely experience, perhaps during downstream

manufacturing processes, and/or during handling, transportation and real-world storage." (*Id.* at 14-18, 15). For example, Exelixis states, "MSN's API and Tablet manufacturing processes utilize heat and humidity that are higher than Dr. Munson's accelerated conditions[,]" which "reinforces that the accelerated conditions are reasonable." (*Id.* at 14-18, 15; *see also id.* at 17 ("During the API manufacturing process, MSN's API is exposed to 55-60°C under high humidity for ~8 hours. … During the subsequent tablet manufacturing process, MSN's API is not refrigerated … and is exposed to heat and humidity at [granulating, drying, and coating steps].")).

I find that Dr. Munson's results from using accelerated conditions are not representative of how MSN's API or tablets will behave in the real world over time. There are significant differences between Dr. Munson's accelerated conditions and the conditions that MSN's API and tablets will face during manufacture and storage.

First, I find that Dr. Munson's accelerated conditions are not representative of the conditions that MSN's API will face during manufacture. (*See id.* at 17 (Exelixis arguing that, during manufacture, "MSN's API is exposed to 55-60°C under high humidity for ~8 hours")). Dr. Munson received samples of MSN's API that had already been manufactured and, thereby, "had already been subjected to eight hours … at 55 to 65 degrees C." (Tr. at 186:11-22). Thus, I find persuasive Dr. Steed's testimony that Form N-2 would already have been present in Dr. Munson's API samples if the API manufacturing conditions caused Form N-2 to form. (See *id.* at 327:20-328:3 (Steed)).

Second, I find that Exelixis has not shown that Dr. Munson's accelerated conditions are representative of MSN's API storage conditions prior to tablet manufacturing. While Dr. Munson let the API sit in open petri dishes at a high temperature and humidity, MSN's ANDA prescribes storing the API "in well closed containers at 2 to 8°C temperature and protect[ed] from moisture."

(PTX-123 at 25; *see* Tr. at 315:18-316:15, 331:3-6 (Steed); *see also Abbott*, 300 F.3d at 1373). Dr. Munson's testimony lacks credibility when he described that his "accelerated conditions are conditions that were going to be slightly higher humidity, slightly higher temperature, something that may be representative of potential storage conditions or also manufacturing conditions." (Tr. at 140:24-141:5 (Munson)). In addition, the samples of MSN's API that Exelixis received were already three years old. (*See* Tr. at 230:8-17 (Munson), 301:20-24 (Steed)). Considering this, I find credible Dr. Steed's testimony that, absent the accelerated conditions, "there's no reason to think that [MSN's three-year old API samples] would begin to convert [to Form N-2]" if left to sit longer at the prescribed storage conditions. (*Id.* at 305:19-306:5 (Steed)).

I also find significant differences between Dr. Munson's accelerated conditions and the conditions that MSN's API undergoes in the subsequent granulating, drying, and coating steps of the tablet manufacturing process.

First, while Dr. Munson applied the accelerated conditions to samples containing only MSN's API, MSN's ANDA requires that MSN's API be combined with excipients before the granulating, drying, and coating steps of tablet manufacturing begin. (*See* PTX-67 at 2-3; Tr. at 316:18-317:1, 320:2-9 (Steed)). I find credible Dr. Steed's testimony that this lack of excipients is significant because "[e]xcipients can act to stabilize an API." (Tr. at 316:18-317:1 (Steed); *see also* Tr. at 323:1-5 (Steed)).

Second, while Dr. Munson exposed MSN's API to 40°C at 75% RH for periods of weeks, the tablet manufacturing steps on which Exelixis relies—the wet granulation (about 3 minutes at up to 25°C and 55% RH), drying (less than 2 hours at up to 40°C and ambient RH), and coating (less than 3 hours at up to 45°C and ambient RH)—differ greatly. (*See id.* at 317:2-323:24 (Steed)). Dr. Munson's accelerated conditions, where the combination of high temperature and

humidity are applied to MSN's API for a dramatically extended period, "are very different conditions" than the conditions MSN's API will experience in the tablet manufacturing process. (*Id.* at 323:21-24 (Steed)).

Third, I do not agree that Dr. Munson's accelerated conditions are representative of the conditions MSN's tablets will likely face. Notwithstanding the fact that Dr. Munson tested MSN's API and not MSN's tablets, MSN's proposed product label requires storing "cabozantinib [(MSN's tablets)] at room temperature between 68°F to 77°F (20°C to 25°C)." (PTX-114 at 24; *see also* Tr. at 339:12-22 (Steed)). MSN's tablets will be stored in sealed bottles at ambient humidity. (*See* Tr. at 342:17-20, 403:16-24 (Steed)). These conditions are in stark contrast to Dr. Munson's accelerated conditions. Further, while Exelixis suggests that MSN may not be able to control its tablets' storage conditions after they enter the chain of commerce (*see* D.I. 308 at 15), I find no persuasive evidence that the storage of MSN's tablets will deviate from those prescribed by its ANDA application and product label. "We cannot assume that [MSN] will not act in full compliance with its representations to the FDA[.]" *In re Brimonidine Pat. Litig.*, 643 F.3d 1366, 1378 (Fed. Cir. 2011).

Considering the strong evidence of significant differences between Dr. Munson's accelerated conditions and the conditions that MSN's API and tablets will likely face, I find that Dr. Munson's test results under accelerated conditions are not representative of how MSN's API will behave in the real world over time.

Exelixis further argues that Dr. Munson's accelerated conditions are in accordance with industry standards for the stability testing of new drugs. (*See* D.I. 308 at 3, 14-17 (citing D.I. 309, ¶¶ 20-21, 54-55)). Particularly, the ICH guidelines explain that "stability testing … provide[s] evidence on how the quality of a drug substance or drug product varies with time under the

influence of a variety of environmental factors such as temperature, humidity, and light[.]" (PTX-739 at Section 1.3; *see also id.* at Section 2.1.7).

While I recognize that the use of stability testing is common practice, I disagree that this justifies Dr. Munson's reliance on his accelerated conditions test results. I find persuasive Dr. Steed's testimony that Dr. Munson's accelerated conditions test results "are [in] no way relevant as a predictor of [the] stability of [MSN's API] because they don't reflect the conditions that [MSN's API] will be subjected [to]." (Tr. at 328:8-13 (Steed); *see also id.* at 314:3-318:10 (Steed)). Indeed, while the ICH guidelines explain that stability studies "can be used to assess longer term chemical effects at non-accelerated conditions[,]" it also warns, "Results from accelerated testing studies are not always predictive of physical changes." (PTX-739 at 13). For example, Dr. Steed identified scientific literature explaining that "[t]he kinetics of phase transformation can become problematic for accelerated stability studies[.]" (DTX-484 (Brittain) at 50). Accelerated conditions may cause "transformation[s] that might not occur in ambient conditions or under storage conditions[.]" (Tr. at 314:12-315:17, 315:14-17 (Steed) (analyzing DTX-484 (Brittain)). These statements cast additional, strong doubts as to the reliability of Dr. Munson's stability study in determining whether MSN's API will convert to Form N-2 over time.

There is another reason the ICH guidelines do not justify Dr. Munson's stability testing. Dr. Munson's accelerated conditions are a far cry from what is recommended by the ICH guidelines. For a refrigerated compound, such as MSN's API, the ICH guidelines recommend accelerated conditions of "25°C ± 2°C/60% RH ± 5% RH." (PTX-739 at 10). The ICH guidelines also state that, for "stability testing of new drug substances[,]" "the stability studies should be conducted on the drug substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution." (*Id.* at 8). In sharp contrast,

Dr. Munson's accelerated conditions involve a higher temperature/humidity and an open container. (*See* Tr. at 333:7-13 (Steed) ("Q. And then you've said accelerated testing is not relevant to your infringement analysis. But even if it was, did Dr. Munson use the right conditions for accelerated testing as prescribed by the ICH guidelines? A. No, the appropriate ICH-accelerated conditions are the low ones, 25 degrees C, 60 percent humidity in a sealed container.")).

To further support its argument that Dr. Munson's accelerated conditions were reasonable, Exelixis also argues that MSN performed stability studies on its API, where the conditions applied, including high humidity/temperature and an open container, were like Dr. Munson's accelerated conditions. (*See* D.I. 308 at 10, 17). I disagree that MSN's stability studies support the reasonableness of Dr. Munson's accelerated conditions. As Dr. Steed credibly explained, the MSN stability studies were intended "to see what might happen if the [manufacturing] process went to extreme sets of conditions" and were performed in the process of developing the tablet manufacturing process. (Tr. at 324:4-325:12, 400:4-10 (Steed)). In that way, MSN's stability studies are not predictive or representative of the conditions MNS's API can be expected to experience in the real world. Nonetheless, the conditions of MSN's stability studies were significantly different than Dr. Munson's accelerated conditions, particularly in terms of duration (24 hours versus multiple weeks). (*See id.* at 324:25-325:25 (Steed)).

Having found that Dr. Munson's ^{13}C NMR testing of MSN's API after applying the accelerated conditions is not "representative of what is likely to be approved and marketed," I further find that Dr. Munson's ^{13}C NMR test results are not persuasive evidence of infringement. *See Merck*, 881 F.3d at 1385. As Dr. Steed explained, Dr. Munson's accelerated conditions expose MSN's API to a "perfect storm" of "all of these conditions … together … for … long … periods of time," whereas "MSN's API and ANDA drug product aren't [exposed] to this perfect

storm of conditions at any point, either during manufacture or … during storage afterwards." (Tr. at 318:4-24 (Steed)). For that reason, "Dr. Munson's stressed accelerated conditions … are [irrelevant] to the inquiry as to whether MSN's proposed product infringes the '776 patent." (*Id.* at 340:8-18 (Steed)).

Relatedly, Exelixis faults MSN for performing "no [^{13}C NMR] testing of its own" that directly rebuts Dr. Munson's testing. (D.I. 308 at 20-21). I find, however, that this is irrelevant. MSN is not burdened with proving non-infringement.

2. Exelixis' Supplementary Use of ^{19}F SSNMR Testing

Exelixis also presented evidence of ^{19}F SSNMR testing performed by Dr. Munson on several batches of MSN's API before and after the application of his accelerated conditions. (*See* D.I. 308 at 18-20). Exelixis argues that differences between these batches in the "rate of conversion" to Form N-2 prove that Form N-2 must have been present in MSN's API before the accelerated conditions were applied. (*See id.*). Exelixis uses this evidence to reason that, even though Dr. Munson only detected Form N-2 in MSN's API via ^{13}C NMR testing after applying accelerated conditions, Dr. Munson's accelerated conditions were not the source of all the Form N-2 that was detected. (*See id.*).

Specifically, like his procedure for ^{13}C NMR testing, Dr. Munson performed ^{19}F SSNMR testing on MSN's API prior to applying accelerated conditions (at "0 weeks") and at set intervals thereafter (at 1, 2, 4, and 8 weeks). (*See id.* at 18-19 (citing D.I. 309, ¶¶ 59-61)). Exelixis explains that ^{19}F SSNMR testing "is a more sensitive technique" than ^{13}C NMR testing for "measuring the presence of Form N-2 in MSN's API." (*Id.* at 19 (citing D.I. 309, ¶ 17)). With ^{19}F SSNMR testing, Dr. Munson did not detect Form N-2 in MSN's API at 0 weeks. (*See id.* at 19 (citing D.I. 309, ¶ 61)). After 0 weeks, however, Dr. Munson detected Form N-2 in several of

the batches of MSN's API. (*See id.* at 19-20 (citing D.I. 309. ¶¶ 61-62)). Dr. Munson testified that each of the tested batches "had different rates of conversion [to Form N-2] which [indicated] that there [were] … different levels of the Form N-2 initially present" in each of the batches. (Tr. At 157:15-23 (Munson)). Thus, Exelixis concludes that the ^{19}F SSNMR test results further support a finding of infringement because they prove that the Form N-2 detected via ^{13}C NMR testing "was also present before accelerated conditions were applied." (D.I. 308 at 20 (citing D.I. 309, ¶¶59-63)).

I disagree on two levels.

First, I am not convinced that the ^{19}F SSNMR test results prove that Form N-2 was present in MSN's API before the accelerated conditions were applied. Dr. Munson testified that he "did not quantify" how much Form N-2 was detected in each batch subject to ^{19}F SSNMR testing and, instead, was able to consider the amount of Form N-2 detected in each batch "with respect to each other[.]" (Tr. at 179:1-13, 221:17-222:7 (Munson)). Dr. Munson explained that his ^{19}F SSNMR testing "was all about detection" because actual quantification was "not an easy thing to do." (Tr. at 221:17-222:7 (Munson)). Considering Dr. Munson's testimony, as well as the fact Dr. Munson did not detect Form N-2 in MSN's API when measuring it at 0 weeks with ^{19}F SSNMR (*see* D.I. 308 at 19 (citing D.I. 309, ¶ 61)), I am not convinced that his methods were sufficiently reliable to be persuasive. Thus, I do not find credible Dr. Munson's conclusion that Form N-2 must have been present in MSN's API before the accelerated conditions were applied.

Second, even if MSN's API contained an undetectable amount of Form N-2 before the accelerated conditions were applied, I find this fact to be insufficient to prove infringement of claim 1. Exelixis' argument regarding Dr. Munson's ^{19}F SSNMR test data is predicated on the theory that "[i]nfringement can be established based on the presence of any amount of Form N-2

in a composition." (D.I. 308 at 7; *see also* Tr. at 232:17-22 (Munson) ("Q. Is it your opinion that the MSN tablet has to have a hundred percent of its API being Form N-2 to fall within the scope of the claim? A. No. Q. How much is needed? A. Any amount.")). This is incorrect. Limitation 1(i) more narrowly requires that sufficient Form N-2 be present for certain peaks to be present in ^{13}C NMR testing. Even if Exelixis had proven based on Dr. Munson's ^{19}F SSNMR testing that MSN's API contained undetectable amounts of Form N-2 prior to Dr. Munson's application of accelerated conditions, this does not prove infringement of claim 1.

Thus, while "circumstantial evidence [can be] sufficient to establish infringement and … direct testing of the finished product is not [always] required" (D.I. 308 at 6), I do not find that Exelixis' arguments based on the ^{19}F SSNMR test data are a persuasive remedy to its failure to provide ^{13}C NMR test results indicating the presence of Form N-2 in MSN's API before the accelerated conditions were applied.[2]

Thus, I find that Exelixis has not proven by a preponderance of the evidence that MSN's API will infringe claim 1 of the '776 patent.

3. Form N-2 in MSN's Tablet

Since Dr. Munson detected Form N-2 in MSN's API, Exelixis argues, "the laws of thermodynamics dictate that it is not possible that form N-2 somehow magically disappears" in

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[2] While only Exelixis performed ^{19}F SSNMR testing, MSN also offered circumstantial evidence that is indicative of non-infringement of claim 1. For example, Dr. Steed performed XRPD testing on MSN's API and found that there was "no evidence of Form N-2 at all." (Tr. at 305:6-10 (Steed); *see also* D.I 319 at 10-11 (citing D.I. 318, ¶¶ 25-29, 41)). I also find credible the testimonies of Dr. Reddy and Dr. Steed that MSN's ANDA specification requires that the XRPD test results of manufactured API be the same as the standard XRPD data for Form S. (*See* Tr. at 253:1-10 (Reddy) (explaining that the specification for producing MSN's tablets requires "compar[ing] [a] sample diffractogram with [a] standard diffractogram to ensure the presence of [the] characteristic peaks [of Form S and to ensure that these diffractograms] match[] fully"), 401:2-9 (Steed) (agreeing that the specification for producing MSN's tablets prevents "future batches of MSN's API [from having] Form N-2 in them without being detected by MSN")).

MSN's tablets. (*Id.* at 4-6, 5-6). To make this point, Exelixis explains, "Form S [is] less stable than Form N-2" and, because of this, "convert[s] over time to the more stable Form N-2." (*Id.* at 8-9 (citing D.I. 309, ¶¶ 59-61)). Thus, Exelixis argues that, because "Form N-2 is in the API[,] … it does not convert to any other form once present in MSN's … Tablet." (*Id.* at 22).

MSN does not directly contest that proving infringement of limitation 1(i) by MSN's API also proves infringement by MSN's tablets. This is immaterial, however, because, as explained above, I do not find that Exelixis has proven by a preponderance of the evidence that Form N-2 is present in MSN's API according to the requirements of limitation 1(i).

4. Induced Infringement

Exelixis argues, "MSN will induce infringement of claim 1 of the '776 patent when it manufactures and supplies the MSN ANDA Products to Zydus for distribution in the United States." (*Id.* at 24-25). As explained above, I find that Exelixis has not proven direct infringement. Considering that there is no direct infringement, I find that Exelixis has not shown by a preponderance of the evidence that MSN will induce infringement of claim 1.

IV. CONCLUSION

MSN failed to prove by clear and convincing evidence that claim 5 of the '473 patent is invalid as obvious. Exelixis failed to prove by a preponderance of the evidence that MSN will infringe claim 1 of the '776 patent.

The parties shall submit a final judgment consistent with this memorandum opinion within one week.